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## Azole-Resistant *Aspergillus fumigatus*, Iran

**To the Editor:** *Aspergillus fumigatus* causes a variety of diseases in humans. The drugs recommended for treatment of *Aspergillus* diseases are the mold-active azole antifungal drugs (1). However, a wide range of mutations in *A. fumigatus* confer azole resistance, which commonly involves modifications in the *cyp51A* gene (2), the target for azole antifungal drugs.

Azole resistance is thought to be selected for as a result of patient therapy or exposure to azole compounds in the environment; resistance in clinical *A. fumigatus* isolates has been increasingly reported in several European countries, Asia, and the United States (3–7). The most frequently reported resistance mechanism is a 34-bp tandem repeat (TR<sub>34</sub>) in combination with a substitution at codon 98 (TR<sub>34</sub>/L98H) (4); this mechanism is believed to have been selected for through environmental exposure to azole fungicides.

Because routine in vitro susceptibility testing of clinical *Aspergillus* isolates is not common in many centers worldwide, the prevalence of azole resistance might be underestimated. We investigated the prevalence of azole resistance in clinical *A. fumigatus* isolates stored for 6 years (2003–2009) at Tehran University Mycology Reference Centre and Islamic Azad University, Ardabil Branch, Iran.

We investigated 124 clinical *A. fumigatus* isolates obtained from patients with *Aspergillus* diseases (online Technical Appendix Table 1, [wwwnc.cdc.gov/EID/article/19/5/13-0075-Techapp1.pdf](http://wwwnc.cdc.gov/EID/article/19/5/13-0075-Techapp1.pdf)). We conducted strain identification, in vitro antifungal susceptibility testing, and sequence-based analysis of the *Cyp51A* gene, as described (4). We performed microsatellite genotyping of all *A. fumigatus* isolates for which the MIC of

itraconazole was  $\geq 16$  mg/L (8) by using a short tandem repeat *A. fumigatus* assay, and we compared the results with those reported for the Netherlands (20 isolates) and other European countries (24 isolates) (online Technical Appendix Figure).

The distribution of azole-resistant and wild-type *A. fumigatus* isolates examined in this study, according to year of isolation, is shown in online Technical Appendix Table 1. Of 124 *A. fumigatus* isolates, 4 grew on the wells containing itraconazole and voriconazole, indicating a multidrug-resistant phenotype. Of these resistant isolates, 3 were from patients with chronic pulmonary aspergillosis and 1 was from a patient with allergic bronchopulmonary aspergillosis (Table).

Sequence analysis of the *CYP51A* gene indicated the presence of TR<sub>34</sub>/L98H in 3 isolates and no mutations in the other isolate (Table). The first TR<sub>34</sub>/L98H isolate had been recovered in 2005, which is relatively early compared with reported isolations in other countries (online Technical Appendix Table 2). Microsatellite typing of 6 short tandem repeat loci demonstrated identical patterns for 2 of the 3 azole-resistant isolates from Iran, but the TR<sub>34</sub>/L98H isolates from Iran did not cluster with those from the Netherlands and other European countries, indicating no close genetic relatedness (online Technical Appendix Figure).

The TR<sub>34</sub>/L98H azole resistance mechanism was first described in 1998 in the Netherlands; since then, its presence in clinical and environmental *A. fumigatus* isolates in multiple European countries and recently in Asia has been increasingly reported (online Technical Appendix Table 2) (3–7). In the study reported here, prevalence of azole resistance in clinical *A. fumigatus* isolates obtained from patients in Iran was 3.2%; most isolates exhibited the TR<sub>34</sub>/L98H resistance mechanism. The fact that the first TR<sub>34</sub>/L98H isolate was found relatively early, in 2005, underscores the possibility that prevalence

Table. Characteristics of 4 azole-resistant clinical *Aspergillus fumigatus* isolates, Iran\*

Isolate	Underlying disease	Previous azole exposure	34-bp tandem repeat†	Amino acid substitution in <i>cyp51A</i> gene‡	MIC, mg/L			
					Amphotericin B	Itraconazole	Voriconazole	Posaconazole
T-IR-AF 12	CPA	Yes	Positive	L98H	0.5	≥16	4.0	0.5
T-IR-AF 17	CPA	No	Positive	L98H	0.5	≥16	4.0	0.5
T-IR-AF 433	CPA	Yes	Negative	ND	0.5	≥16	8.0	0.5
T-IR-AF 890	ABPA	No	Positive	L98H	0.5	≥16	8.0	0.25

\*CPA, chronic pulmonary aspergillosis; ND, not detected; ABPA, allergic bronchopulmonary aspergillosis.

†34-bp tandem repeat in the promoter region of *CYP51A* gene.

‡The numbers indicate the position at which an amino acid change occurs. Nucleotides are numbered from the translation start codon ATG of *cyp51A*.

of azole resistance might be underestimated in many countries because in vitro susceptibility testing of *A. fumigatus* is not routinely performed.

Microsatellite genotypic analysis of *A. fumigatus* isolates from the Netherlands and various European countries showed that the genetic diversity of TR<sub>34</sub>/L98H isolates is lower than that of wild-type controls (8). It has been suggested that TR<sub>34</sub>/L98H isolates might have a common ancestor that developed locally and subsequently migrated across Europe. In contrast, genotyping of TR<sub>34</sub>/L98H originating from India suggested a different dynamic; all environmental and clinical TR<sub>34</sub>/L98H isolates from India shared the same multilocus microsatellite genotype not found in any other analyzed samples, from within India or from the Netherlands, France, Germany, or the People's Republic of China (9). The molecular epidemiology of the TR<sub>34</sub>/L98H isolates from Iran suggests that they cluster apart from the European isolates, indicating that migration from Europe to Iran, or vice versa, is unlikely. Genotyping of more TR<sub>34</sub>/L98H isolates from the Middle East and comparison with those from India would enhance understanding of the origin and geographic spread of TR<sub>34</sub>/L98H.

Our study indicates that TR<sub>34</sub>/L98H was in Iran in 2005; this finding adds to the growing list of regions where acquired resistance in *A. fumigatus* of environmental origin is documented. From a global perspective, fungicide use is second highest in the Asia-Pacific regions (24%), preceded only by western Europe (37%) (10).

For a better understanding of the scale of this emerging public health problem and for insight into the dynamics of geographic migration, surveys of fungal culture collections for TR<sub>34</sub>/L98H and molecular typing studies are warranted. These data would be useful not only for clinical management of *Aspergillus* diseases but also for enabling policy makers to develop strategies that prevent resistance selection by the environmental route.

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## Search for Possible Additional Reservoirs for Human Q Fever, the Netherlands

**To the Editor:** Q fever is a zoonosis caused by the bacterium *Coxiella burnetii*. The Q fever outbreak in the Netherlands affected ≈4,000 humans during 2007–2010 (1). In this outbreak, 1 genotype of *C. burnetii*

appeared to be responsible for abortions in small ruminants and for clinical disease in humans (2,3). However, little is known about the outbreak genotype and the prevalence of *C. burnetii* in possible additional reservoirs for human Q fever (i.e., cats, dogs, horses, sheep, and cattle) in the Netherlands.

We aimed to search for possible additional reservoirs for human Q fever in the Netherlands. Placentas from 15 cats, 54 dogs, and 31 horses were collected in 2011 at 5 veterinary practices. Placentas were collected by targeted sampling at breeding facilities and during parturition with veterinary assistance. In addition, 27 ovine, 11 caprine, 16 porcine, 8 equine, and 139 bovine placentas (originating from aborting animals from throughout the Netherlands that were submitted in 2011 to investigate the abortion cause) were included in the study. Samples were stored at –20°C before testing.

DNA was extracted from the allantochorion of the placenta and analyzed as described (2). Samples with sufficient DNA load (cycle threshold [ $C_t$ ] value <32) were typed by using 2 multilocus variable-number tandem-repeat analyses (MLVA) genotyping methods (MLVA-12 and MLVA-6), and the multispacer sequence typing method (3–5). Two *C. burnetii* strains from the Netherlands representing the outbreak genotype (X09003262, 3345937) and the Nine Mile RSA 493 were included as reference. For prevalence calculations, the Netherlands was divided in a southern part, comprising the Q fever hot spot area of notified cases in humans and small ruminants during the 2007–2010 epidemic (1,6), and a northern part, comprising the rest of the country.

*C. burnetii* DNA was not detected in placentas from cats, goats, or pigs. *C. burnetii* DNA was detected in 4 (7% [95% CI 0.4–14.4]) of 54 canine placentas; 3 from the north and 1 from the south of the Netherlands. *C. burnetii* DNA was detected in 3 (8% [95% CI 0.0–16.1]) of 39 equine placentas, all

from the north of the country, without known abortion history. *C. burnetii* DNA was detected in 7 (26% [95% CI 9.4–42.5]) of 27 ovine and in 33 (24% [95% CI 16.7–30.8]) of 139 bovine placentas. The prevalence of *C. burnetii* DNA-positive ovine and bovine placentas from the north and the south did not differ significantly.

The *C. burnetii* DNA load in the placentas from dogs ( $C_t$  value 37.4–38.0) and horses ( $C_t$  value 35.4–37.4) was too low to be suitable for genotyping. Typing of 1 positive sheep sample resulted in an incomplete genotype, which is related to the outbreak genotype (sheep 192, Figure). Seven of the 33 *C. burnetii* DNA-positive bovine placentas were suitable for typing. One sample had a genotype similar to the outbreak genotype (2,3). Six other samples revealed a (partial) genotype related to bovine genotypes from the Netherlands (2,5,7), including a novel one. MLVA-6 and multispacer sequence typing results were consistent with the MLVA-12 results (Figure).

Results give no indication for major reservoirs of *C. burnetii* in cats, goats, and pigs in the Netherlands in 2011. However, the low numbers of placentas may have biased the results. Dogs and horses should be considered as reservoirs for *C. burnetii*. The detection of *C. burnetii* DNA-positive placentas in dogs and horses in the northern part of the country indicates the presence of a true reservoir rather than a spillover effect from the contaminated environment in the south. This observation is consistent with a reported seroprevalence of 13% in dogs in the Netherlands in 1992 (1). Until now, horses had been discussed as a risk factor in the Q fever outbreak in the Netherlands (8).

Prevalence data from sheep and cattle suggest that *C. burnetii* is present in placentas in 25% of the abortion cases in these species. Presence of the outbreak genotype of *C. burnetii* in sheep has been observed (2,5), indicating sheep are a reservoir for Q fe-

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## Technical Appendix

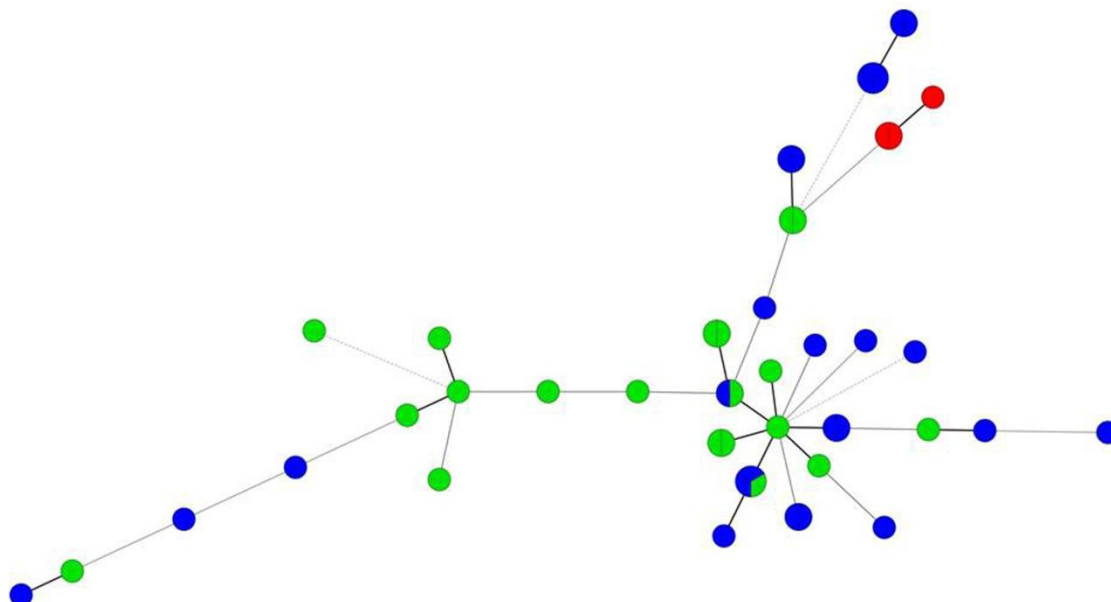
Technical Appendix Table 1. Distribution of azole-resistant and azole-susceptible *Aspergillus fumigatus* isolates, Iran, 2003–2009

Year of isolation	No. isolates with each phenotype and resistance mechanism		
	Wild type	Resistant, TR <sub>34</sub> /L98H	Resistant, non-TR <sub>34</sub> /L98H
2003	11	–	–
2004	18	–	–
2005	11	1	–
2006	17	–	–
2007	19	2	1
2008	20	–	–
2009	24	–	–
Total	120	3	1

Technical Appendix Table 2. First reports of multiple-triazole-resistant *Aspergillus fumigatus* isolate(s) carrying the TR<sub>34</sub>/L98H mutations in the CYP51A gene, by country

Region/Country	First reported TR <sub>34</sub> /L98H <i>A.fumigatus</i> isolate(s)	Reference
<b>Europe</b>	Netherlands	1998
	UK	1999
	Norway	2001
	Spain	2002/2003
	Denmark	2007
	Belgium	2008
	France	2010/2011
	Germany	2012
		Burgel et al. 2012 (6), Morio et al. 2012 (7)
<b>Asia</b>	Iran	2005
	India	2008
	China	2008/2009
		Present study
		Chowdhary et al. 2012 (9,10)
		Lockhart et al. 2011 (11)





Technical Appendix Figure. Minimum spanning tree comparing genotypic relatedness of clinical azole-resistant *Aspergillus fumigatus* isolates carrying TR<sub>34</sub>/L98H alteration in the *CYP51A* gene from Iran with those reported from European countries. Microsatellite typing of 6 STR loci demonstrated identical patterns for two of the three azole-resistant isolates from Iran, but the TR<sub>34</sub>/L98H isolates from Iran did not cluster with those from the Netherlands and other European countries, indicating no close genetic relatedness. Each circle corresponds to a unique genotype, and each color indicates the origin of azole-resistant TR<sub>34</sub>/L98H isolates: red, Iran (n = 3); green, the Netherlands (n = 20); blue, other European countries (n = 24). The size of the circle corresponds to the number of isolates with that genotype. Connecting lines correspond to the number of different microsatellite loci between the genotypes: solid thick and thin branches indicate 1 and 2 microsatellite marker differences, respectively; dashed branches indicate 3 microsatellite marker difference; dotted branches indicate  $\geq 4$  microsatellite marker differences between genotypes.

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